General

Guideline Title

Venous thromboembolism diagnosis and treatment.

Bibliographic Source(s)

Dupras D, Bluhm J, Felty C, Hansen C, Johnson T, Lim K, Maddali S, Marshall P, Messner P, Skeik N. Venous thromboembolism diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. 90 p. [216 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Venous thromboembolism diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 Jan. 96 p.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guidance, refer to Summary of Changes Report -- January 2013. In addition, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as a method of assessing the quality of evidence and writing recommendations. This document is in transition to the GRADE methodology. Transition steps incorporating GRADE methodology for this document include the following:

- Priority placed upon available systematic reviews in literature searches.
- All existing Class A (randomized controlled trials [RCTs]) studies have been considered as high quality evidence unless specified differently by a work group member.
- All existing Class B, C and D studies have been considered as low quality evidence unless specified differently by a work group member.
- All existing Class M and R studies are identified by study design versus assigning a quality of evidence. Refer to Crosswalk between ICSI Evidence Grading System and GRADE (see below in the "Definitions" section).
- All new literature considered by the work group for this revision has been assessed using GRADE methodology.

The recommendations for venous thromboembolism are presented in the form of three algorithms with 41 components, accompanied by detailed annotations. Algorithms are provided in the original guideline document at the ICSI Web site for Deep Vein Thrombosis (DVT) Diagnosis; Pulmonary Embolism (PE) Diagnosis; and Venous Thromboembolism (VTE) Treatment. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (Low Quality, Moderate Quality, High Quality, Meta-analysis, Systematic Review, Decision Analysis, Cost-Effectiveness Analysis, Guideline, and Reference) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights

- A clinical pretest probability assessment should be completed in patients with suspected VTE. (*Annotations #4, 17; Aim #1*)
- D-dimer can be used as a negative predictor to eliminate need for further testing. (*Annotations #6, 12, 22; Aim #1*)
- Confirm diagnosis of lower extremity DVT with imaging study, preferably duplex ultrasound. (*Annotation #9; Aim #1*)
- In patients with a high clinical pretest probability for PE, begin anticoagulation without delay. (*Annotation #18; Aim #1*)
- Achieve rapid effective anticoagulation. (*Annotation #32; Aim #2*)
- In patients with acute VTE, heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) or fondaparinux should be given for at least 5 days and until the international normalized ratio (INR) is ≥2.0 for 2 consecutive days. (*Annotation #32, 33; Aim #2*)
- Arrange for home therapy in appropriate patients. (*Annotation #36; Aim #4*)

Deep Vein Thrombosis (DVT) Diagnosis Algorithm Annotations

1. Clinical Suspicion of VTE?
   Perform an appropriate physical examination and obtain a history to evaluate for DVT.

   Among patients with pain and swelling of the leg, some will have DVT. Recent unilateral swelling and pain above or below the knee without explanatory bone or joint trauma is suspicious for DVT *[Low Quality Evidence]*.

   As part of the evaluation, record onset, location, and character of patient's leg pain and swelling.

   Factors increasing risk include:

   - Patient's history of past VTE, family history of VTE
   - Pregnancy, postpartum or current estrogen use
   - Recent trauma or surgery
   - Immobilization
   - Presence of cancer
   - Varicosities
   - Airline flight longer than 8 hours

   Exam findings may include erythema, warmth, and superficial thrombophlebitis with a palpable tender cord over a superficial vein. In the most severe form, phlegmasia cerulea dolens, the venous drainage of the lower extremity, is acutely and severely obstructed, threatening limb viability. This may require other treatment (see Annotation # 41, "Other Interventions").

   It is well known that clinical findings are poor predictors of the presence or severity of thrombosis; therefore, determining pretest probability is necessary in managing the diagnostic process *[Guideline]*.

4. Determine Clinical Pretest Probability (CPTP)
   Recommendation:

   - Clinicians should use a formal protocol to determine a patient's clinical pretest probability (CPTP) of DVT.

   This can guide the choice of test(s) needed to triage patients for this condition, which can have minimal signs and symptoms but lead to serious consequences if left untreated. Please refer to Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis," in the original guideline document for an example of a CPTP model protocol.

5. Low Clinical Pretest Probability
   Recommendation:

   - In patients with low CPTP of DVT, clinicians should obtain a D-dimer.

   Patients with a low score, such as a score of zero on Wells scoring, can be safely managed by testing for D-dimer. If D-dimer is negative, duplex ultrasound can be omitted, and repeat ultrasound is not needed in one week unless new or progressive clinical symptoms occur *[Guideline], [Low Quality Evidence]*.

6. D-dimer above Cutoff?
   High sensitivity D-dimer assays have high negative predictive value for patients with a low clinical pretest probability of DVT or PE.

   The D-dimer test is most helpful in outpatients with suspected DVT or PE. The negative predictive value of the D-dimer is lower in patients

with recent surgery, trauma, cancer and those in post-partum period.

Refer to the original guideline document for more information about D-dimer.

7. DVT Excluded — Consider Other Diagnosis
Patients with a low clinical pretest probability of DVT and a negative D-dimer assay have a very low (less than 2%) risk of subsequent finding of DVT. These patients can be followed clinically with no further evaluation unless warranted by new or progressive clinical symptoms *[Low Quality Evidence]*.

8. Moderate/High Clinical Pretest Probability
Recommendations:

- Clinicians should do a venous duplex ultrasound (DUS) as the first test in patients with moderate or high CPTP.
- If the DUS is negative, clinicians should obtain a D-dimer to guide further testing needs.

Patients with moderate or high CPTP have a 15% to 70% risk of DVT. Because of the high incidence of DVT in this population, DUS should be ordered as the first test, and D-dimer assay can be used after a negative DUS result to determine further radiologic testing needs.

10. Duplex Ultrasound Positive?
Recommendation:

- Patients with a low clinical pretest probability (CPTP) of DVT and a positive D-dimer assay should undergo a DUS to confirm the diagnosis of DVT.

DUS is considered to be the primary diagnostic test for evaluation of proximal DVT. The ability to diagnose DVT may vary depending on the proximity of the suspected DVT site. In addition, the interpretation of the DUS can be difficult in patients with a previous history of DVT. Consider consulting with the interpreting clinician.

In 1995, Wells found that 24% of the cases with high CPTP and negative ultrasound had DVT on venography. Extra testing would be needed in only 20% of high-risk cases, because 80% were diagnosed on ultrasound. The high-risk group represented only 16% of all cases presenting for possible DVT. In low CPTP risk cases with negative ultrasound, only 1% had DVT on venography. (See Annotation #1, "Clinical Suspicion of Venous Thromboembolism [VTE]?")

Proximal (Popliteal Vein and Above)

DUS is considered to be the primary diagnostic test and should be the first choice for evaluation *[Guideline]*, *[Low Quality Evidence]*. The most recent CHEST guideline recommends against routinely using magnetic resonance imaging (MRI) or computed tomography (CT) venography in patients with suspected first lower extremity DVT *[Guideline]*.

Calf (below Popliteal Vein)

Some calf thrombi can be found by DUS. However, a negative test cannot exclude an isolated calf DVT *[Low Quality Evidence]*.

11. Deep Vein Thrombosis Confirmed – See Venous Thromboembolism Treatment Algorithm
Recommendations:

- Clinicians should treat proximal thrombosis with anticoagulation unless contraindicated.
- Clinicians should treat calf vein thrombosis with anticoagulation or follow with serial DUS to rule out proximal progression.

Proximal Thrombosis (at or Above the Popliteal Vein)

Proximal thrombosis should be treated with anticoagulation unless contraindicated *[Guideline]* (see Annotation #31, "Complicated Venous Thromboembolism or Comorbidities?"). Additional information can be found in the NGC summary of the ICSI Antithrombotic Therapy Supplement.

Calf Thrombosis (Below the Popliteal Vein)

Increasing evidence suggests that patients with symptomatic calf DVT benefit from treatment similar to that for proximal DVT. Thrombosis of the calf veins is common and carries significant risk of propagation, including propagation into the proximal deep veins *[Guideline]*, *[Low Quality Evidence]*, *[Moderate Quality Evidence]*. If not treated, these patients should be followed by serial DUS to rule out proximal progression of thrombus to popliteal vein. Short-term treatment with LMWH and compression stockings was not shown superior to compression alone in a randomized controlled trial *[High Quality Evidence]*.

Following patients with suspected thrombosis limited to the calf veins, and treating with anticoagulation only for proximal extension on serial studies, may be an acceptable alternative to anticoagulation. However, the safety of this approach in patients with confirmed symptomatic calf DVT has not been studied *[Guideline]*, *[Low Quality Evidence]*.

Shared Decision-Making

See Appendix E, "ICSI Shared Decision-Making Model," in the original guideline document.

12. D-dimer above Cutoff?
Recommendation:

- Clinicians should not administer anticoagulation to patients with a negative ultrasound and a negative high sensitivity D-dimer.

It is safe to withhold anticoagulation among outpatients with a negative duplex ultrasound and a "negative" high sensitivity D-dimer (measured by whole blood latex agglutination or enzyme-linked immunoassay, respectively) *[Guideline]*, *[Low Quality Evidence]*.

13. Follow-Up Studies/Second Duplex Ultrasound or Venography
Recommendation:

- Clinicians should consider venography or repeat ultrasound in 3 to 7 days if there is high CPTP of a DVT in the setting of a positive D-dimer and negative DUS.

The combined use of CPTP and DUS is effective in confirming or excluding the diagnosis of DVT in the majority of cases. Please refer to Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis," in the original guideline document. If clinical suspicion of DVT is high and ultrasound is negative, consider further testing, such as repeat ultrasound for suspected calf thrombosis, or venography for suspected proximal thrombosis in three to seven days.

- Serial Ultrasonography
When calf thrombosis is suspected but the initial ultrasound is negative, serial ultrasound is an acceptable alternative to venography. Furthermore, ultrasonography appears to be superior to impedance plethysmography for this purpose *[Guideline]*, *[Low Quality Evidence]*, *[High Quality Evidence]*. If a thrombus is discovered, anticoagulation is recommended.

- CT Venography of the Inferior Vena Cava and the Iliac Veins
This is performed at some institutions to visualize proximal obstructions. The common, superficial, and deep femoral veins can be done as well. CT venography does not include the distal calf veins. Newer diagnostic techniques, spiral contrast CT and magnetic resonance venography, have shown excellent results in preliminary studies. Currently these techniques could be considered in patients with unusual diagnostic situations, including suspected iliocaval clots or in patients with contraindications for venography *[Low Quality Evidence]*.

- Contrast Venography (Proximal, Intra-abdominal)
This is generally considered the historical gold standard for the accurate diagnosis. However, it has numerous drawbacks including cost, discomfort to the patient, significant resource use, limited availability, requirement of foot vein cannulation, use of intravenous contrast, and secondary thrombi. For these reasons, venography is generally reserved for difficult diagnostic cases. It may be considered when the DUS is non-diagnostic in the setting of suspected recurrent DVT *[Guideline]*.

Pulmonary Embolism (PE) Diagnosis Algorithm Annotations

(This Pulmonary Embolism Diagnosis Algorithm does not apply to pregnant patients.)

14. Clinical Signs/Symptoms of PE
Consider PE in patients who present with dyspnea, pleuritic chest pain, and tachypnea.

Less frequent signs/symptoms are cough, hemoptysis, fever, syncope, diaphoresis, non-pleuritic chest pain, apprehension, rales, increased pulmonic component of the second heart sound (^S_2P), wheezing, hypotension, tachycardia, cyanosis, or pleural rub. Massive PE can present with hemodynamic instability or cardiac arrest. Clinical findings are nonspecific and should not be used as the only criteria to diagnose PE *[High Quality Evidence]*, *[Low Quality Evidence]*.

15. Clinically Unstable?
Patients who are clinically unstable may have massive PE, which is associated with up to a tenfold increase in mortality. Massive PE should be considered when any of the following clinical signs are present: hemodynamic instability (including systolic blood pressure less than 90 mm Hg, or a drop in 40 mm Hg), syncope, severe hypoxemia or respiratory distress. Massive PE can also be identified with severely

abnormal imaging studies: computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan that shows 50% or more absent perfusion or an echocardiogram showing right ventricular (RV) failure or strain. Furthermore, elevated troponin and brain natriuretic peptide (BNP) levels are associated with RV strain, and elevations of both have been associated with increased mortality, even in the absence of overt hemodynamic compromise *[Guideline]*.

The challenge is to identify the group of patients with an increased risk of mortality and consider whether they are candidates for thrombolytic therapy. Since thrombolytic therapy has not been clearly shown to improve mortality in any group of patients, its use is always a clinical judgment. Nevertheless, most experts consider thrombolytic therapy lifesaving if the patient is clinically unstable as defined above *[Guideline]*. Other groups of patients who are candidates for consideration of thrombolytic therapy are those with a high clot burden on imaging studies and/or RV failure or strain on echocardiogram *[High Quality Evidence]*. Lastly, a preliminary recommendation would be to measure a BNP and/or troponin in any patient with a clinical presentation that is concerning *[Low Quality Evidence]*, *[Meta-analysis]*, in order to identify apparently stable patients at higher risk for poor outcome *[Guideline, Low Quality Evidence]*.

17. Estimate Clinical Pretest Probability (CPTP)?
Recommendation:

- Clinicians should calculate the CPTP of PE.

Patients presenting with signs and symptoms of PE need:

- Complete history and physical exam. Risk factor assessment for venous thromboembolic disease plays a role in determining the pretest probability of PE. Risk factors include previous history of VTE, recent surgery, immobilization, paresis, personal or family history of inheritable thrombophilic disorder or personal history of acquired thrombophilia (e.g., antiphospholipid antibody, cancer, estrogen, pregnancy or myeloproliferative disorder).
- Estimate pretest probability. The work group continues to recommend the Wells criteria, but other prediction rules exist, none having proved itself superior to Wells *[Guideline]*, *[Low Quality Evidence]*. The clinical evaluation can also lead to suspicion of an alternative diagnosis. Careful review and application of the pretest probability model by all clinicians are recommended.
- Chest x-ray, arterial blood gases, electrocardiogram (EKG) and other tests as indicated for alternative diagnoses considered.

A simplified clinical pretest probability scoring system may improve diagnostic accuracy by being easy to use consistently and alerting clinicians to the need for further testing *[Guideline]*, *[Low Quality Evidence]*.

18. Clinical Pretest Probability High (Score >6); Begin Anticoagulation
Recommendation:

- Clinicians should begin anticoagulation without delay, unless contraindicated, if the CPTP score is high (six or more on Wells' criteria).

If the clinical pretest probability score is high, begin parenteral anticoagulation therapy promptly *[Guideline]*. For a patient with heparin induced thrombocytopenia (HIT), consider argatroban or danaparoid. Lepirudin will no longer be manufactured after May 2013 (see Appendix B, "Model for Predicting Clinical Pretest Probability for Pulmonary Embolism," in the original guideline document).

19. Clinical Pretest Probability Low (Score ≤4) (PERC Optional)
Recommendation:

- If the CPTP score is less than or equal to four, and if the clinician considers the patient at low risk of PE, then the clinician may perform the Pulmonary Embolism Rule-Out Criteria (PERC) assessment to identify patients at very low risk PE (see Annotation #20, "Pulmonary Embolism Rule-Out Criteria [PERC] Positive?").

20. Pulmonary Embolism Rule-Out Criteria (PERC) Positive?
Recommendation:

- The clinician may perform PERC assessment to identify group at very low risk of pulmonary embolism (PE).

If any of these questions is answered yes, then the patient is considered PERC positive:

- Is the patient older than 49 years?
- Is the patient's pulse >99 beats/minute?
- Is the patient's pulse oximetry reading <95% while breathing room air?
- Does the patient have hemoptysis?
- Is the patient on exogenous estrogen? Does the patient have prior diagnosis of venous thromboembolism?
- Has the patient had surgery or trauma (requiring endotracheal intubation or hospitalization) in the previous four weeks?

- Does the patient have unilateral leg swelling at the calves?

[Guideline]

There is concern that since D-dimer testing is not very specific for the diagnosis of PE. Use of this test in very low risk populations leads to a high false-positive rate and subsequently exposure of low-risk persons to testing that likely includes ionizing radiation. In view of this fact, there has been effort to consider ways to limit advanced testing to those who have a higher CPTP.

Refer to the original guideline document for more information regarding PERC.

22. D-dimer Above Cutoff?
    In patients with "PE Less Likely," the Christopher Study Investigators found that patients with negative D-dimer levels could safely be observed without further investigation, as the incidence of non-fatal VTE was 0.5% in the subsequent three months. This data is consistent with other studies *[Low Quality Evidence]*. In this group it is safe to withhold anticoagulation therapy and follow these patients clinically.

    The specificity of the D-dimer may be reduced if the duration of symptoms or signs of VTE exceed 2 or 3 days prior to testing. The sensitivity may be reduced if the patient has been receiving heparin therapy or has had a recent procedure, trauma or surgery. In these settings, as well as the postpartum period, there may be increases in the plasma D-dimer level. A diagnostic imaging study for DVT or PE (e.g., DUS [with compression] of the leg, high-resolution chest CT angiography) may be more effective. Studies have also suggested that the negative predictive value of D-dimer may be lower in patients with cancer *[Low Quality Evidence]*, distal DVTs *[Low Quality Evidence]* and previous DVTs *[Low Quality Evidence]*.

    If the D-dimer is positive, further evaluation is necessary to adequately exclude a PE.

23. Pulmonary Embolism Unlikely – Consider Other Diagnosis
    Evaluate patients for other diagnoses when PE has been excluded. No additional workup is needed in patients with an unlikely clinical pretest probability with a positive D-dimer and negative CTPA.

    Patients with a negative D-dimer and PE Less Likely CPTP have a low incidence of PE *[High Quality Evidence]*, *[Low Quality Evidence]*. It is safe to withhold anticoagulation therapy and follow these patients clinically *[Systematic Review]*.

    Patients with a negative CTPA and PE Less Likely CPTP and positive D-dimer results can safely have PE excluded and be followed clinically in the outpatient setting *[Low Quality Evidence]*, *[High Quality Evidence]*.

    Patients with persistent symptoms or symptoms that progressively worsen should have further diagnostic testing. Duplex ultrasound should be used to improve the clinical likelihood of diagnosing VTE disease and avoid more invasive testing.

    Patients who have had PE excluded need to have the evaluation for other diagnoses completed and appropriate treatment and follow-up initiated. In particular, pericarditis, myocardial infarction, and pneumonia should be excluded in appropriate circumstances. When performed, CTPA will frequently help identify alternative causes such as pericardial effusion, pneumonia and pleural effusion.

25. Computed Tomographic Pulmonary Angiography (CTPA) Positive?
    Recommendation:

    - Clinicians should obtain a CTPA as the next diagnostic test.

    CTPA is the first line study of choice unless a contraindication exists, then V/Q scan would be preferred. V/Q imaging follows a different diagnostic algorithm (see Appendix C, "Ventilation/Perfusion [VQ] Lung Imaging Algorithm and Annotations," in the original guideline document for more information).

    The choice of initial imaging study depends on several factors including how readily available the tests are, the resolution of images obtained, underlying illnesses/conditions including renal status of the patient, and experience of the radiologists. In some institutions, CTPA is easier to obtain than a V/Q scan. CTPA is also more useful in patients with underlying cardiac disease and chronic obstructive pulmonary disease/asthma. When alternative diagnoses are likely, CTPA is especially good, as it can rule out PE and confirm other diagnoses with one test.

    Non-invasive pulmonary vascular imaging studies are recommended as the initial diagnostic evaluation in most patients with suspected PE. Both V/Q scans and CTPA have a relatively high degree of specificity when they are read respectively as "high probability" scan results or "positive" for PE. A negative V/Q scan also has a high degree of specificity. However, either a non-diagnostic (intermediate or low radiologic probability scan results) or a negative CTPA suffer from lack of sensitivity and usually require further diagnostic studies. In rare instances the CPTA may miss a clot. V/Q scanning is not always readily available and other pulmonary processes, such as chronic

obstructive pulmonary disease and congestive heart failure, can influence its specificity *[Low Quality Evidence]*, *[High Quality Evidence]*, *[Guideline]*.

CTPA has a high sensitivity and specificity for central clots. The sensitivity and specificity drop substantially for peripheral clots. CTPA is also more useful in patients with underlying cardiac disease and chronic obstructive pulmonary disease/asthma. When alternative diagnoses are likely, CTPA is especially good, as it can rule out PE and confirm other diagnoses with one test. CTPA showing positive results for segmental/subsegmental embolism should be followed up with additional testing, due to the increase in false-positives. With state-of-the-art equipment, the ability to exclude peripheral clots is probably increasing, but the clinical probability must guide the decision to pursue further testing (compression ultrasound or pulmonary angiography).

For patients with CT scan results that cannot clearly confirm or rule out the possibility of PE due to the patient's condition and comorbidities or due to scan technical limitation, clinicians should review the CPTP and D-dimer results to determine what further work up may be indicated *[Guideline]*, *[Low Quality Evidence]*, *[High Quality Evidence]*, *[Systematic Review]*.

Recent evidence convincingly demonstrates that a negative CTPA effectively rules out PE. When current generation multi-detector CT scanning is used, 3 months after negative CTPA, the incidence of recurrent VTE is 1.2% *[Systematic Review]*. This compares very favorably to the 1.7% recurrence rate at 3 months of standard pulmonary angiography, the long recognized gold standard. Bilateral DUS of the leg is recommended to improve the diagnosis of VTE without performing invasive tests. Pulmonary angiography can be considered if clinical suspicion remains high or the patient's condition deteriorates *[Low Quality Evidence]*, *[High Quality Evidence]*.

The risks associated with a misdiagnosis of PE are typically more severe than those associated with a misdiagnosis of DVT. Higher negative predictive values are required to safely use D-dimer to exclude PE. The evidence to date suggests that current assays, with the possible exception of enzyme-linked immunoassay (ELISA) and rapid ELISA methods, are not acceptable for use in excluding PE in patients with clinical suspicion of PE *[Guideline]*.

A positive ultrasound usually confirms the diagnosis of DVT and requires treatment regardless of the presence or absence of PE. When DUS is negative, the incorporation of CPTP can improve diagnostic accuracy and potentially avoid unnecessary pulmonary angiography. Several studies of DUS performed after non-diagnostic V/Q scans have shown that pulmonary angiography can be avoided in 15% to 40% of patients when DVT is identified.

CPTP is an important adjunct to DUS at this point. In cases of suspected PE, where non-invasive tests do not confirm its presence, pulmonary angiography should be performed *[Low Quality Evidence]*, *[Cost Effectiveness Analysis]*.

26. Order/Review D-dimer
Recommendation:

    - Clinicians should consider the CPTP and D-dimer results to guide additional testing in patients with a non-diagnostic or negative CTPA.

    If D-dimer has not yet been obtained, order the test at this point.

28. Duplex Ultrasound Positive?
Recommendation:

    - Clinicians should use venous DUS to assess for VTE in patients with negative lung imaging results.

    In patients with negative CTPA results and positive D-dimer and a PE Likely clinical probability, further evaluation with DUS should be used to improve clinical likelihood of diagnosing disease and avoid more invasive testing.

29. Pulmonary Embolism Confirmed – See Venous Thromboembolism Treatment Algorithm
Recommendation:

    - Clinicians should treat symptomatic and asymptomatic PE according to the Venous Thromboembolism (VTE) Treatment Algorithm.

    Patients with a positive CTPA scan and PE Likely CPTP are essentially confirmed positive for PE. They can be considered for treatment with no further diagnostic testing *[High Quality Evidence]*, *[Low Quality Evidence]*, *[Guideline]*.

    Pulmonary emboli are noted as incidental findings in 1% to 4% of chest CT studies ordered for other reasons. This is more frequent in patients who have studies done for follow-up/staging of malignancies *[Low Quality Evidence]*. Further testing may be helpful to confirm acute VTE disease such as D-dimer, venous studies, etc. Asymptomatic PE should be treated with the same protocol as outlined for symptomatic PE *[Guideline]*.

31. Complicated Venous Thromboembolism or Comorbidities?
Treatment should be individualized for patients with complicated venous thromboembolism (VTE) or specific comorbidities (see below).

Massive Pulmonary Embolism

Massive PE has up to a tenfold greater mortality than standard PE; thus, the evaluation and treatment are individualized. Massive PE should be considered in a patient with any hemodynamic instability, severe hypoxemia or respiratory distress. CTPA, V/Q scan, or standard pulmonary angiography that shows occlusion of 50% or more of the pulmonary vasculature should prompt consideration of massive PE, as well. In this group of patients, BNP and troponin testing, combined with echocardiography, can help identify patients who are at high risk of deterioration and thus would be candidates for thrombolytic therapy. A recent study has also suggested that there may be some benefit for the use of thrombolytics in submassive PE. In this circumstance, specialty consultation and consideration of thrombolytics may be appropriate *[Guideline]*, *[High Quality Evidence]*, *[Systematic Review]*, *[Low Quality Evidence]*.

Patients with severe hemodynamic compromise may require immediate thrombolytic therapy. In this group of unstable patients, bedside echocardiography can be used as the only diagnostic tool, and thrombolytic therapy can be given without imaging the pulmonary arteries. When thrombolytic therapy is contraindicated, patients should be considered for thrombectomy (either catheter-directed or open) or inferior vena cava (IVC) filter placement.

Contraindications to Anticoagulation

Absolute contraindications would include patients with active severe hemorrhage or recent intracranial hemorrhage. Relative contraindications include recent or imminent surgery, trauma, anemia (hematocrit less than 30), renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease, and liver disease *[High Quality Evidence]*, *[Systematic Review]*.

These patients require more intense monitoring for bleeding complications if given anticoagulation therapy. If not treated with anticoagulation therapy, serial ultrasounds for untreated calf DVT, or IVC filters for proximal DVT are indicated. (See Annotation #41, "Other Interventions.") Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on contraindications to anticoagulation.

Known History of Heparin-Induced Thrombocytopenia (HIT)

Thrombocytopenia can complicate heparin therapy. Both a non-immune and a more serious immune-mediated platelet-associated immunoglobulin G (IgG) reaction, HIT, have been described. If the patient has previously received heparin, especially within the past 3 months, thrombocytopenia may occur within hours or days *[Low Quality Evidence]*.

Patients with a history of HIT should not be treated with either UFH or LMWH. In those without thrombosis, argatroban, lepirudin, or danaparoid are preferred initial therapy *[Guideline]*. However, lepirudin will no longer be manufactured by May 2013. Fondaparinux may be an option; it has little or no anti-platelet effects, and has been used successfully to mitigate the effects of HIT. However, several cases of fondaparinux-associated HIT have been reported (see Annotation #41, "Other Interventions"). Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on HIT. See also the American College of Chest Evidence-Based Clinical Practice Physicians Guidelines 2012 Supplement *[Guideline]*.

Extensive Iliofemoral Thrombosis/Phlegmasia

Patients found to have extensive iliofemoral disease or evidence of phlegmasia will likely require inpatient monitoring and longer course of anticoagulation therapy than patients with uncomplicated DVT. Thrombolytic therapy may be of benefit in these patients for possible reduction of post-thrombotic complications (see Annotation #41, "Other Interventions").

Pregnancy

Pregnancy is out of the scope of this guideline.

Familial Bleeding Disorders

Because of the complexity and controversy surrounding the use of standard anticoagulation to treat DVT in patients with familial bleeding disorders, these patients are excluded from the guideline. There is little data that has addressed the use of LMWH in these patients. Although treatment for these patients may be similar to that found in the algorithm, the work group felt that these patients should be treated individually and not be included in the guideline.

Severe Renal Dysfunction (Creatinine Clearance Less Than 30 mL/minute)

These patients require closer monitoring for bleeding complications and dosing adjustments if LMWH is used. Patients with significant renal impairment (creatinine clearance less than 30 mL/min) can accumulate LMWH. Significant adjustments need to be made for these patients. Pharmacy consultation is recommended.

Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on anticoagulation therapy in patients with renal dysfunction.

32. Initiate Anticoagulation
Recommendations:

- Clinicians should initially treat PE with UFH, LMWH or fondaparinux *[Guideline]*.
- Clinicians should initially treat most patients diagnosed with DVT with LMWH or fondaparinux *[Guideline]*.
- Clinicians may consider rivaroxaban for the initial treatment of both PE and DVT without additional anticoagulation *[Moderate Quality Evidence]*, *[Low Quality Evidence]*.

UFH, LMWH, or fondaparinux are preferred for the initial treatment of patients with PE or DVT. LMWH and fondaparinux are as safe and as effective as continuous UFH. Suitable patients can be safely treated with LMWH and fondaparinux in the outpatient setting.

Rivaroxaban has also recently received U.S. Food and Drug Administration (FDA) approval for the initial treatment of both PE and DVT; however, its role in clinical practice has yet to be determined. It is an oral agent which facilitates management without hospitalization in selected patients.

Heparin/fondaparinux should be continued for at least 5 days after the initiation of warfarin therapy and until International Normalized Ratio (INR) is ≥2.0 for two consecutive days.

LMWH

Treatment for VTE with LMWH provides reliable anticoagulation levels when given subcutaneously on a weight-based dosing schedule. No laboratory monitoring of the intensity of anticoagulation is required for LMWH, except in special circumstances.

For patients with underlying cancer, LMWH may be the preferred initial anticoagulant and has been shown to decrease the risk of recurrent VTE when used long term compared to vitamin K antagonists *[High Quality Evidence]*.

Please note that LMWH may not be appropriate for patients with renal insufficiency (creatinine clearance less than 30 mL/min) because studies have shown modestly delayed clearance in patients with chronic renal failure. The clinician should weigh this evidence when considering outpatient therapy *[Low Quality Evidence]*. (See Annotation #31, "Complicated Venous Thromboembolism or Comorbidities?")

The decision for hospital or home therapy is not mutually exclusive. A patient could be started on LMWH in the hospital and discharged to continue therapy at home at any time during the course of therapy *[Guideline]*.

UFH

UFH is administered by continuous intravenous infusion following a bolus dose. HIT is a recognized complication of UFH therapy (see Annotation #41, "Other Interventions").

Refer to the original guideline document for more information on UFH.

Fondaparinux

Fondaparinux, a sodium pentasaccharide, is administered by subcutaneous injection once daily for the treatment of DVT and PE. Fondaparinux has a long half-life of 17 to 21 hours, with no known antidote, and some encourage caution in patients at higher risk of bleeding complications. Other precautions include the elderly, renal insufficiency, and patients weighing less than 50 kg. The usual dose is 5 mg once daily for patient less than 50 kg, 7.5 mg once daily for patients 50 to 100 kg, or 10 mg once daily for patients over 100 kg. Fondaparinux treatment should be continued for at least five days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0). Warfarin should be initiated as soon as possible, usually within 72 hours.

The heparin assay (anti-factor-Xa) has been used to monitor effects of fondaparinux; however, new calibrators other than heparin will need to be established. A platelet count should be obtained prior to the initiation of fondaparinux. Antibodies to fondaparinux rarely interact with

Platelet Factor 4. There are several reports of HIT with fondaparinux (see the NGC summary of ICSI's Antithrombotic Therapy Supplement). Additional platelet monitoring is not required.

Rivaroxaban

Rivaroxaban is a direct factor X inhibitor that has been FDA approved for the initial treatment of both PE and VTE. It has been shown that rivaroxaban is non-inferior to warfarin in the management of acute VTE based on Einstein and Einstein PE trials *[Moderate Quality Evidence]*, *[Low Quality Evidence]*. Recommended treatment for the first 21 days is 15 mg twice a day, followed by 20 mg once daily.

HIT

Both UFH and LMWH are associated with HIT. HIT is an immune-mediated reaction to heparins. It occurs in 2% to 3% of patients treated with UFH and less than 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH.

Monitoring platelet counts during treatment with UFH or LMWH may be individualized based on the risk for HIT in an individual patient *[Guideline]*. HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin.

Delayed-onset HIT is an increasingly recognized form of this disorder. The possibility of delayed-onset HIT should be considered in any patient presenting with thromboembolism after a recent hospitalization.

Patients suspected of having any form of HIT should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for patients with HIT. Several agents are FDA approved: lepirudin, argatroban, and most recently, bivalirudin *[Low Quality Evidence]*, *[Guideline]*. However, lepirudin will no longer be manufactured after May 2013.

If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped to decrease the risk of limb gangrene. The warfarin effect should be reversed with vitamin K, and DTI therapy should be initiated. Low-maintenance doses of warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a five-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes *[Guideline]* (see Annotation #41, "Other Interventions," for more information).

Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on LMWH, UFH, fondaparinux, synthetic pentasaccharides, DTI and rivaroxaban, and HIT.

33. Maintenance Anticoagulation
Recommendations:

- A goal INR of 2.5 (range 2.0-3.0) is recommended for patients with VTE.
- Clinicians should generally use warfarin for continued anticoagulation.
- Clinicians should use LMWH for patients with VTE in the setting of cancer.
- Clinicians may consider using rivaroxaban for continued anticoagulation.
- Start heparin/fondaparinux and warfarin at the same time. Heparin (UFH or LMWH) and/or fondaparinux should be given for a minimum of five days and continued until INR ≥2.0 for two consecutive days.

Warfarin

Warfarin therapy should be begun at the same time as heparin/fondaparinux and continued for a minimum of five days and until the INR is ≥2.0 for two consecutive days. The anticoagulant effect of warfarin is delayed until clotting factors already circulating are cleared. Although Factor VII has a shorter half-life in the blood (six to seven hours), peak anticoagulant activity is delayed for up to 96 hours until factors with longer plasma half-lives (II, IX and X) have cleared *[Low Quality Evidence]*.

Therapy should be initiated with a dose of 5 mg (less in patients with risks for increased sensitivity to warfarin), with dosage adjustments based on results of INR testing. Clinicians may consider the use of 10 mg for the first two doses to assist in determining the warfarin maintenance dose *[Low Quality Evidence]*.

A goal INR of 2.5 (range 2.0-3.0) is recommended for the treatment of patients with VTE *[Guideline]*.

Warfarin is recommended over LMWH for long-term therapy *[Guideline]*. In patients with VTE and cancer who are not treated with LMWH, warfarin is suggested over dabigatran or rivaroxaban for long-term therapy *[Guideline]*.

Low-Molecular-Weight Heparin

For patients with VTE who are not treated with warfarin, LMWH is recommended over dabigatran or rivaroxaban for long-term therapy *[Guideline]*. LMWH is also recommended over warfarin for long- term treatment of patients with VTE in the setting of cancer *[Guideline]*.

Rivaroxaban

Rivaroxaban has recently been approved by the FDA for treatment of VTE and PE based on recent trials *[Moderate Quality Evidence]*, *[Low Quality Evidence]*.

Other Agents

Dabigatran is a direct thrombin inhibitor that has been shown to be non-inferior to warfarin for the management of acute VTE based on the RECOVER trial *[Moderate Quality Evidence]*; however, at the time of this revision, the FDA had not approved it for generalized treatment of VTE (see the NGC summary of the ICSI Antithrombotic Therapy Supplement for additional information.)

Special Patient Populations

In patients with suspected hypercoagulable state (Protein C or Protein S deficiency), the patient should be adequately anticoagulated with UFH or LMWH and/or fondaparinux before warfarin is started at a low dose (2-5 mg). This is to avoid warfarin-induced skin necrosis or other transient hypercoagulable complications *[Low Quality Evidence]*.

The NGC summary of the ICSI's Antithrombotic Therapy Supplement contains additional information on warfarin therapy.

34. Outpatient Treatment Appropriate?
Patients with uncomplicated VTE may be considered for outpatient therapy with LMWH and warfarin *[Guideline]*.

Patients presenting with symptomatic PE and decreased cardiorespiratory reserve should initially be treated in the hospital.

Inclusion criteria for outpatient therapy:

- Patient has good cardiorespiratory reserve
- Patient has no excessive bleeding risks
- Patient's creatinine clearance is greater than 30 mL/minute

However, because of the need for an organized support system and time-of-day considerations for home care agencies, many patients may need hospitalization during the first 24 hours to start therapy promptly.

Other considerations include:

- Patients need to be taught how to administer the drug and recognize complications.
- Daily INRs will be needed to guide the institution of warfarin therapy. The warfarin dose will need to be adjusted to the INR.
- Patients will need resources to answer questions and deal with problems.

[Guideline], *[Low Quality Evidence]*, *[High Quality Evidence]*

Patient-focused care would include shared-decision making between patient, family and the clinician when deciding upon outpatient treatment. According to the Minnesota Shared Decision-Making Collaborative: Shared Decision-Making is a process in which patients and clinicians collaborate to clarify all acceptable options, ensure the patient is well-informed, and choose a course of care consistent with patient values and preferences and the best available medical evidence. Please refer to Appendix E in the original guideline document, "ICSI Shared Decision-Making Model."

35. Inpatient Treatment
Therapy is discussed in Annotation #32, "Initiate Anticoagulation," and in Annotation #33, "Maintenance Anticoagulation."

36. Outpatient Protocol
Recommendation:

- Clinician should prescribe graduated compression stockings (not T.E.D.s™) to provide more rapid resolution of pain and swelling for

the patient *[Guideline]*.

All Stable VTE Patients

- Daily self-administered injections, caregiver-administered injections, or daily clinic visits. The patient will need to be geographically accessible to have INRs drawn and receive care for problems that arise.
- Daily INR for transitioning to warfarin treatment after 2 days of adequate anticoagulation. (For details, see the NGC summary of ICSI's Antithrombotic Therapy Supplement)
- Duration of anticoagulation to be individualized, see Annotation #40, "Continued Anticoagulation with Follow-Up and Secondary Prevention."

DVT Patients

- If the criteria in Annotation #34, "Outpatient Treatment Appropriate?" can be met, DVT treatment can be started in the outpatient setting; otherwise, hospitalize until teaching, medication, and close follow-up can be assured.
- For DVT, use graduated compression stockings, at least 30 to 40 mm Hg (not T.E.D.™ stockings) on the affected leg to reduce the risk of post-phlebitic syndrome. Stockings are contraindicated for patients with peripheral artery disease.
- Graduated compression stockings combined with early ambulation do not cause any increase in PE and give more rapid resolution of pain and swelling.

For management of patients with chronic post-thrombotic syndrome, please see Annotation #40, "Continued Anticoagulation with Follow-Up and Secondary Prevention."

Please refer to the NGC summary of the ICSI's Antithrombotic Therapy Supplement for a discussion of complications during anticoagulation therapy.

37. Patient Education
    Instruct patients on the use of anticoagulants. Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on patient education. Patient education materials are also available (see the Quality Improvement Support section in the original guideline document).

38. Complications During Therapy?
    Treatment should be individualized for patients who develop complications.

    Suspect HIT if platelets drop 50% or more from baseline.

    Patients with complications of therapy should be identified and treated individually rather than by a standard guideline.

    Patients who have bleeding, thrombocytopenia, or osteoporosis may require individual adjustments in therapy. HIT should be suspected if the platelet count drops 50% or more from baseline labs.

    Patients on warfarin therapy who experience bleeding or skin necrosis, or who become pregnant may require individual adjustments in therapy.

    Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on potential complications of anticoagulation therapy.

    [Low Quality Evidence]

39. Anticoagulation Failure?
    Recommendations:

    - Clinicians should use objective measures to determine anticoagulation failure.
    - Clinicians should consider fondaparinux if a patient fails on warfarin or heparin therapy (UFH or LMWH).
    - Clinicians should consider inferior vena cava filter in selected cases.

    Recurrent symptomatic DVT or PE during adequate heparin (UFH or LMWH), fondaparinux or warfarin treatment represents failure of treatment and needs objective documentation, especially as a new DVT may be difficult to distinguish from post-phlebitic syndrome.

    Active cancer is the most common cause of warfarin failure *[Low Quality Evidence]*, *[Moderate Quality Evidence]*.

    Antiphospholipid antibodies may be the cause of anticoagulant failure. In these patients, recurrence was most likely in the six months following cessation of warfarin, and higher INRs of greater than or equal to 3.0 were more effective than 2 to 3. Aspirin did not help *[Low Quality Evidence]*.

In certain circumstances, alternate treatment such as an inferior vena cava (IVC) filter may be indicated. If a patient fails on warfarin therapy, UFH or LMWH or fondaparinux may need to be reinstituted. The work group felt these patients should be identified and treated individually rather than by a standard guideline. The 9th American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy provided the following recommendations regarding placement of an IVC filter:

- For most patients with DVT, the ACCP recommends against the routine use of an IVC in addition to anticoagulants.
- In PE or proximal DVT patients with a contraindication for or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate anticoagulation, the ACCP suggests placement of an IVC filter.
- Patients with distal (calf vein) thrombosis may have anticoagulation stopped but do not likely need IVC filter given their low risk of embolization.

[Guideline]

40. Continued Anticoagulation with Follow-up and Secondary Prevention
Recommendations:

- Clinicians should individualize the duration of anticoagulation therapy.
- Clinicians should prescribe graduated compression stockings (not T.E.D.s™) to decrease the risk of post-phlebitic syndrome.

Duration of Anticoagulation

Most VTE episodes are treated adequately with three to six months of anticoagulation, after which time an individualized assessment of risk of recurrence should be made. The initial duration of warfarin anticoagulation must be individualized depending on risks of (VTE) recurrence and risk of a complication (e.g., bleeding) due to warfarin therapy. The 9th ACCP Consensus Conference on Antithrombotic Therapy recommends *[Guideline]*:

- Transient risk/provoked (e.g., surgery, immobilization, estrogen use, trauma): 3 months.
- Idiopathic risk/unprovoked: 3 to 6 months
    - Patients with documented antiphospholipid antibodies or two or more thrombophilic conditions should be treated for 3 to 6 months and considered for indefinite anticoagulation therapy.
    - Patients with documented deficiency of antithrombin, protein C or S, factor V Leiden, prothrombin 20210 mutation, homocysteinemia, or high factor VIII conditions should be treated for 3 to 6 months and considered for indefinite anticoagulation therapy.
- Recurrent disease or continued risk factors: indefinite
    - Patients with cancer should be initially treated for 3 to 6 months with LMWH and then with anticoagulation therapy indefinitely or until the cancer is resolved.
    - Patients with two or more episodes of documented DVT should receive anticoagulation therapy indefinitely.

[Guideline], *[Meta-analysis]*, *[Systematic Review]*

Refer to the original guideline document for more information on duration of coagulation and risk factors for recurrent VTE in patients with unprovoked DVT.

Anticoagulation Management

A coordinated effort for follow-up of patients started on warfarin is required to minimize the risks of both hemorrhagic and thrombotic complications while on treatment. In the first several weeks of anticoagulation, INRs need to be checked at least weekly. After stabilization, the interval between INRs can be increased from weekly to biweekly, up to but not beyond 4 weeks *[Low Quality Evidence]*, *[Moderate Quality Evidence]*. However, the most recent ACCP statement suggested that in selected patients, the interval could be extended to 12 weeks *[Systematic Review]*.

A goal INR target of 2.5 is recommended for the majority of patients who are kept on long-term anticoagulation. Patients who have recurrent VTE on adequate anticoagulation with warfarin may require a higher target INR (e.g., 3.0). One study suggested protection against recurrence in patients who were initially treated for 6 to 12 months at the target INR of 2.5, then treated to an INR range of 1.5 to 2.0. However, a recent study comparing long-term anticoagulation at INR 2.5 versus INR 1.5 to 2.0 showed greater protection against recurrence with the higher target INR of 2.5 *[High Quality Evidence]*.

Anticoagulation clinics and computerized dosing programs have helped in the management and monitoring of patients on warfarin therapy. The ACCP published a Best Practices Statement in the most recent update. "We suggest that health care clinicians who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing,

tracking, follow-up, and good patient communication of results and dosing decisions."

Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on establishing and maintaining anticoagulation clinics.

Prevention of Post-Thrombotic Syndrome (Post-Phlebitic Syndrome)

The post-thrombotic syndrome (PTS) is the most common complication of lower extremity DVT, occurring in 20% to 50% of patients. The syndrome is typically an under recognized, under diagnosed, and an under treated condition. Clinically, the symptoms are characterized by chronic leg pain, swelling, fullness and heaviness that can have a significant impact on activities of daily living. Long-term sequelae include development of venous hypertensive ulcerations, which can be recalcitrant to standard treatment and often recurrent. Additional late physical signs include chronic lower extremity edema, hyperpigmentation, lipodermatosclerosis and development of varicose veins *[Low Quality Evidence]*. Without adequate recognition and treatment of PTS, patients may develop significant disabilities and a subsequent inability to perform daily activities of living, including gainful employment.

Standardized treatment includes initiation of 30 to 40 mm Hg weight knee-high or thigh-high compression stockings (not T.E.D.S™) for management of the acute symptoms, and continued for a minimum of two years or longer if patients have persistent symptoms of PTS *[Guideline]*, *[Systematic Review]*. Subsequent long-term utilization of graduated compression stockings (not T.E.D.S™) is standard of care for patients who develop chronic PTS symptoms. Additional treatments include obtaining an ideal body mass index (BMI) and participation in a regular exercise regime that maintains an adequate calf muscle pump function.

Refer to the original guideline document for more information on long-term complications of DVT.

Look for Malignancy?

Some patients who present with idiopathic DVT may have occult malignancy. However, extensive work-ups in asymptomatic patients beyond appropriate cancer screening have not shown benefit *[Moderate Quality Evidence]*.

In patients with known cancer, risk of DVT is increased. In patients who have idiopathic DVT, there may be cancer present at the time of presentation in 3% to 12% of cases. A routine complete medical examination (including history, physical examination [including pelvic, rectal and breast examination], complete blood count, sedimentation rate, renal and liver function tests, urinalysis and chest x-ray) was deemed adequate to detect cancer.

Thrombophilia

Certain patients should be tested for thrombophilia. If done, this testing should be done 2 weeks after discontinuation of anticoagulation *[Low Quality Evidence]* (see the original guideline document for laboratory test values prevalent in patients with DVT). The work group recommends consideration be given to a discussion with a thrombophilia expert for:

- Patients who have recurrent thromboembolic disease
- Patients with first idiopathic DVT who:
    - Are less than 50 years of age
    - Have a family history of VTE among one or more first-degree relatives
    - Have an unusual site of spontaneous thrombosis
    - Have massive venous thrombosis

Activity Level

There is no evidence that restriction of activity is of benefit nor is there evidence to determine the appropriate activity level. The clinician needs to be guided by individual patient circumstances, including pain and swelling.

Ambulatory exercise programs are unlikely to exacerbate symptoms and may result in improved leg muscle flexibility *[Low Quality Evidence]*.

41. Other Interventions*
*Other interventions may include IVC filters, serial calf ultrasound, HIT therapy, thrombolytic therapy and surgery.

Recommendations:

- Clinicians should consider IVC filters, thrombolytic therapy or surgical thrombectomy in selected patients.
- Clinicians should treat HIT with DTIs.

- Clinicians may order serial ultrasounds to follow patients with untreated calf thrombosis.

IVC Filters

Treatment is required due to risk of mortality. Accepted indications for IVC interruption include:

- Patients with PE or proximal DVT and contraindications to anticoagulation
- Progressive thromboembolism, despite *adequate* anticoagulation
- Patients with underlying pulmonary hypertension in whom a PE would likely be fatal

Consultation with a specialist is strongly recommended prior to placement of a filter, as long-term sequelae of filter placement include increased risks of recurrent DVT and PE.

IVC filter is the procedure of choice in patients with a contraindication or complication of anticoagulation, who are at high-risk for proximal vein thrombosis, who experience recurrent thromboembolism despite adequate anticoagulation, who have chronic recurrent PE with pulmonary hypertension, or who are undergoing pulmonary embolectomy or pulmonary endarterectomy.

Retrievable filters have made short-term placement possible for patients with transient contraindications to anticoagulation therapy. However, the ICSI work group's clinical experience shows retrievable filters, in practice, are removed less than one fourth of the time. An audit at one center found that follow-up for retrievable filter placements was inadequate. Failure to remove the filter was documented in 15% of the cohort *[Low Quality Evidence]*. Filter placement does not provide treatment for existing VTE, when safe, anticoagulation should be considered.

Intravenous Thrombolytic Therapy

Lytic therapy has been used in patients with extensive iliofemoral disease who demonstrate evidence of vascular compromise (phlegmasia). Lytic therapy has the potential to reduce the long-term post-phlebitic consequences of proximal DVT through early thrombolysis, restoration of patency, and preservation of venous valve function. Catheter-directed lytic therapy is preferred over systemic lytic therapy. This therapy may be a means of reducing the incidence of PTS. However, long-term randomized studies comparing this therapy to standard anticoagulation have not been performed. Management should be individualized and is most appropriate for patients with massive iliofemoral thrombosis. Consultation with a specialist is strongly recommended prior to initiation of lytic therapy *[Guideline]*, *[Low Quality Evidence]*, *[Systematic Review]*.

Thrombolytic therapy results in more rapid clot resolution, but it does not significantly reduce mortality or the risk of recurrent PE in hemodynamically stable patients *[Systematic Review]*, *[High Quality Evidence]*. Pooled data show thrombolytic therapy has an increased incidence of major hemorrhage and intracranial hemorrhage as compared to UFH therapy alone. Elevated diastolic blood pressure is a risk factor for intracranial hemorrhage *[Moderate Quality Review]*, *[Systematic Review]*, *[Low Quality Evidence]*.

Surgical Thrombectomy

In a highly select group of patients, surgical venous thrombectomy has been utilized. These patients typically have extensive venous thrombosis and have contraindications for anticoagulation and lytic therapy. Surgical thrombectomy has historically been utilized to reduce acute symptomatology in patients with iliofemoral thrombosis and was touted to reduce the risk of post-phlebitic syndrome development *[Low Quality Evidence]*. Management should be individualized. The morbidity and mortality associated with this surgical procedure deems it be a procedure of last choice.

Serial Ultrasound in Calf DVT

Serial ultrasound (at 3 and 7 days) may be useful to evaluate for propagation of thromboses in two groups of patients:

- Patients with a positive diagnosis of a calf thrombosis, but contraindications to anticoagulation therapy
- Patients with clinical suspicion of calf thrombosis, but initial negative ultrasound. In general, patients with symptomatic calf DVT who do not have contraindications to anticoagulation will do better if treated similar to those with a proximal DVT *[Moderate Quality Evidence]*.

It is safe to withhold anticoagulation in patients with whom serial compression ultrasound is negative over 5 to 7 days, provided the initial study includes the femoral vein, the popliteal fossa, and scanned to the trifurcation of the calf veins *[Low Quality Evidence]*.

Although serial compression ultrasound testing is safe, it is often inconvenient for patients and healthcare providers, and may not be cost-effective. When patient follow-up cannot be guaranteed, serial compression ultrasound protocols should not be utilized *[Low Quality Evidence]*, *[High Quality Evidence]*, *[Guideline]*.

Treatment of HIT

Patients developing HIT while on heparin therapy should be taken off all UFH and LMWH. DTIs have been used to treat HIT successfully. DTIs approved for the treatment of HIT include argatroban and bivalirudin. Lepirudin will no longer be manufactured in May 2013. DTIs must be administered by continuous intravenous infusion necessitating hospitalization. DTI therapy must be monitored by measuring the activated partial thromboplastin time *[Low Quality Evidence]*.

Please refer to the NGC summary of ICSI's Antithrombotic Therapy Supplement for more information on HIT.

Definitions:

Crosswalk between ICSI Evidence Grading System and GRADE

ICSI GRADE System	Previous ICSI System	
High, if no limitation	Class A:	Randomized, controlled trial
Low	Class B:	[observational]
		Cohort study
	Class C:	[observational]
		Non-randomized trial with concurrent or historical controls
Low		Case-control study
Low		Population-based descriptive study
*Low		Study of sensitivity and specificity of a diagnostic test
*Following individual study review, may be elevated to Moderate or High depending upon study design		
	Class D:	[observational]
Low		Cross-sectional study
		Case series
		Case report
Meta-analysis	Class M:	Meta-analysis
Systematic Review		Systematic review
Decision Analysis		Decision analysis
Cost-Effectiveness Analysis		Cost-effectiveness analysis
Low	Class R:	Consensus statement
Low		Consensus report
Low		Narrative review
Guideline	Class R:	Guideline

ICSI GRADE System	Previous ICSI System	
Low	Class X:	Medical opinion

Evidence Definitions

High Quality Evidence = Further research is very unlikely to change confidence in the estimate of effect.

Moderate Quality Evidence = Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low Quality Evidence = Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain.

In addition to evidence that is graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a Reference throughout the document.

Clinical Algorithm(s)

Detailed and annotated clinical algorithms are provided in the original guideline document for:

- Deep Vein Thrombosis (DVT) Diagnosis
- Pulmonary Embolism (PE) Diagnosis
- Venous Thromboembolism (VTE) Treatment
- Ventilation/Perfusion (V/Q) Lung Imaging (Appendix C)

Scope

Disease/Condition(s)

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE)

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Pulmonary Medicine

Radiology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To assist clinicians and institutions with an evidence-based approach to the diagnosis and acute management of venous thromboembolism (VTE)
- To improve accurate diagnosis and treatment of venous thromboembolism (VTE)
- To prevent progression or recurrence of thromboembolic disease
- To improve safe use of anticoagulants to reduce the likelihood of patient harm and complications of anticoagulation therapy
- To increase the percentage of patients who are evaluated for medication reconciliation upon change in level of care and/or upon discharge.

Target Population

Adult patients age 18 and over with venous thromboembolism (VTE), excluding those with familial bleeding disorders or pregnancy

Interventions and Practices Considered

Deep Vein Thrombosis (DVT)

1. Physical examination, and patient history
2. Clinical pretest probability
3. D-dimer assays
4. Duplex ultrasound
5. Serial ultrasonography or venography
    - Computed tomographic
    - Contrast

Pulmonary Embolism (PE)

1. Assessment of patient's clinical signs and symptoms
2. Clinical pretest probability
    - Complete history and physical examination
    - Chest x-ray, arterial blood gases, electrocardiogram (EKG)
3. Pulmonary Embolism Rule-Out Criteria (PERC)
4. D-dimer test
5. Computed tomographic pulmonary angiography (CTPA)
6. Duplex ultrasound

Venous Thromboembolism (VTE)

1. Consideration of VTE or comorbidities
2. Anticoagulation:
    - Low-molecular-weight heparin (LMWH)
    - Unfractionated heparin (UFH)
    - Fondaparinux
    - Rivaroxaban
    - Heparin-induced thrombocytopenia (HIT)
    - Direct thrombin inhibitors, including dabigatran
3. Maintenance anticoagulation
4. Outpatient treatment
5. Patient education
6. Follow-up and secondary prevention
    - Continued anticoagulation
    - Graduated compression stockings
    - Prevention of post-thrombotic syndrome, thrombophilia
7. Consideration of other interventions in select patients
    - Inferior vena cava (IVC) filters
    - Intravenous thrombolytic therapy
    - Serial calf ultrasound
    - Surgical thrombectomy

Major Outcomes Considered

- Sensitivity, specificity, positive/negative predictive value, and utility of diagnostic tests
- Patient signs and symptoms
- Recurrence rate of thrombosis
- Mortality
- Complications of treatment (e.g., bleeding, heparin-induced thrombocytopenia)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A consistent and defined process is used for literature search and review for the development and revision of the Institute for Clinical Systems Improvement (ICSI) guidelines. Literature search terms for the current revision of this document include diagnosis and treatment of venous thromboembolism, pulmonary embolism, deep vein thrombosis, anticoagulants, outpatient management of anticoagulation, and shared decision-making in PubMed from January 2010 through August 2012. The search was limited to systematic reviews, meta-analyses and randomized control

trials.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Following a review of several evidence rating and recommendation writing systems, Institute for Clinical Systems Improvement (ICSI) has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Crosswalk between ICSI Evidence Grading System and GRADE

ICSI GRADE System	Previous ICSI System	
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In addition to evidence that is graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a Reference throughout the document.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

New Guideline Development Process

A work group consisting of 6 to 12 members that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and an Institute for Clinical Systems Improvement (ICSI) staff facilitator develops each document. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 members may be recruited from medical groups, hospitals, or other organizations that are not members of ICSI. Patients on occasion are invited to serve on work groups.

The work group will meet for 7 to 8 three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and footnotes and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 24 months as indicated by changes in clinical practice and literature. For documents that are revised on a 24-month schedule, ICSI checks with the work group on an annual basis to determine if there have been changes in the literature significant enough to cause the document to be revised earlier or later than scheduled. For yearly reviewed documents, ICSI checks with every work group 6 months before the scheduled revision to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Literature Search

ICSI staff, working with the work group to identify any new pertinent clinical trials, systematic reviews, or regulatory statements and other professional guidelines, conduct a literature search.

Revision

The work group will meet for 1 to 2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

A second review by members is indicated if there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations. If a review by members is not needed, the document goes to the appropriate steering committee for approval according to the criteria outlined in the "Description of Method of Guideline Validation" field.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed published cost analyses.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Critical Review Process

The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Document Approval

Each document is approved by the Committee for Evidence-Based Practice (CEBP).

The committee will review and approve each guideline/protocol, based on the following criteria:

- The aim(s) of the document is clearly and specifically described.
- The need for and importance of the document is clearly stated.
- The work group included individuals from all relevant professional groups and had the needed expertise.

- Patient views and preferences were sought and included.
- The work group has responded to all feedback and criticisms reasonably.
- Potential conflicts of interest were disclosed and do not detract from the quality of the document.
- Systematic methods were used to search for the evidence to assure completeness and currency.
- Health benefits, side effects, risks and patient preferences have been considered in formulating recommendations.
- The link between the recommendation and supporting evidence is clear.
- Where the evidence has not been well established, recommendations based on community practice or expert opinion are clearly identified.
- Recommendations are specific and unambiguous.
- Different options for clinical management are clearly presented.
- Clinical highlights and recommendations are easily identifiable.
- Implementation recommendations identify key strategies for *health care systems* to support implementation of the document.
- The document is supported with practical and useful tools to ease *clinician* implementation.
- Where local resource availability may vary, alternative recommendations are clear.
- Suggested measures are clear and useful for quality/process improvement efforts.

Once the document has been approved, it is posted on the ICSI Web site and released to members for use.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is classified for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of venous thromboembolism

Potential Harms

Diagnosis

- The risks associated with a misdiagnosis of pulmonary embolism (PE) are typically more severe than those associated with a misdiagnosis of deep vein thrombosis (DVT). Higher negative predictive values are required to safely use D-dimer to exclude pulmonary embolism.
- There is concern that since D-dimer testing is not very specific for the diagnosis of PE. Use of this test in very low risk populations leads to a high false-positive rate and subsequently exposure of low-risk persons to testing that likely includes ionizing radiation.

Treatment

- Thrombocytopenia can complicate heparin therapy. Both a non-immune and a more serious immune-mediated platelet-associated immunoglobulin G (IgG) reaction, heparin-induced thrombocytopenia (HIT), have been described. If the patient has previously received heparin, especially within the past 3 months, thrombocytopenia may occur within hours or days.
- Patients on unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux therapy who have bleeding, thrombocytopenia, or osteoporosis may require individual adjustments in therapy. HIT should be suspected if the platelet count drops 50% or more from baseline labs.
- Patients with severe renal dysfunction require closer monitoring for bleeding complications and dosing adjustments if LMWH is used. Patients with significant renal impairment (creatinine clearance less than 30 mL/min) can accumulate LMWH. Significant adjustments need to be made for these patients. Pharmacy consultation is recommended.
- Patients on warfarin therapy who experience bleeding, skin necrosis, or who become pregnant, may require individual adjustments in therapy. In patients with suspected hypercoagulable state (protein C or protein S deficiency), the patient should be adequately

anticoagulated with UFH or LMWH and/or fondaparinux before warfarin is started at a low dose to avoid warfarin-induced skin necrosis or other transient hypercoagulable complications.
- Fondaparinux has a long half-life of 17 to 21 hours, with no known antidote, and some encourage caution in patients at higher risk of bleeding complications. Other precautions include the elderly, renal insufficiency, and patients weighing less than 50 kg.
- Thrombolytic therapy has an increased incidence of major hemorrhage and intracranial hemorrhage as compared to UFH therapy alone.
- The morbidity and mortality associated with surgical thrombectomy deem it to be a procedure of last choice.
- Consultation with a specialist is strongly recommended prior to placement of an inferior vena cava (IVC) filter, as long-term sequelae of filter placement include increased risks of recurrent DVT and PE.

Contraindications

Contraindications

- Absolute contraindications to anticoagulation would include patients who have active severe hemorrhage or recent intracranial hemorrhage. Relative contraindications include recent or imminent surgery, trauma, anemia (hematocrit less than 30), renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease, and liver disease.
- Patients with a history of HIT should not be treated with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).
- Graduated compression stockings are contraindicated for patients with peripheral artery disease.

Qualifying Statements

Qualifying Statements

- The information contained in this Institute for Clinical Systems Improvement (ICSI) Health Care Guideline is intended primarily for health professionals and other expert audiences.
- This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.
- This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.

Implementation of the Guideline

Description of Implementation Strategy

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

- Implement a defined anticoagulation management program to individualize the care provided to each patient receiving (anticoagulation) therapy.
- Clinics and Hospitals: Develop systems for monitoring the effects of anticoagulation to include monitoring of outpatient therapy.
    - Use of standardized practices/protocols that include patient involvement.
- When unfractionated heparin is administered intravenously and continuously, the organization should use programmable infusion pumps.
- Develop systems for providing patient/family education that includes the importance of follow-up monitoring, compliance issues, dietary restrictions, and potential adverse drug reactions and interactions.
    - Patient education to include documentation of the patient's own awareness of his/her risk for venous thromboembolism (VTE) signs and symptoms of VTE and when/how to seek treatment, and demonstrated understanding of the prescribed anticoagulation regimen.
- Develop a policy for providing organizational education regarding anticoagulation therapy to prescriber(s), staff, patients and families.
- Develop protocols for the initiation and maintenance of anticoagulation therapy appropriate to the medication used, to the condition being treated, and to the potential for drug interactions.

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

Quality Measures

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Related NQMC Measures

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with suspected VTE who have a clinical pretest probability (CPTP) assessment completed.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients suspected of DVT who have leg duplex ultrasound (DUS) performed, despite a low clinical pretest probability (CPTP) and a negative D-dimer test.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients diagnosed with lower extremity VTE who meet the criteria for LMWH and for whom shared decision-making was used prior to implementing therapy.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE treated with LMWH who receive heparin treatment for at least five days after the initiation of warfarin therapy and until INR is greater than or equal to 2.0 for two consecutive days.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE treated with UFH who receive heparin treatment for at least five days after the initiation of warfarin therapy and until INR is greater than or equal to 2.0 for two consecutive days.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of adult patients with DVT who have been assessed for the need for graduated compression stockings (not T.E.D.s™).

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE who develop PE.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of VTE patients who have a high clinical pretest probability (CPTP) (score greater than 6) for PE who received anticoagulation prior to diagnostic evaluation.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of hospitalized patients with VTE who receive warfarin on day one of heparin therapy.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE who are initially prescribed warfarin therapy with documentation in the medical record indicating a baseline INR was obtained.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE who receive ongoing warfarin therapy with documentation in the medical record indicating a current INR is available and is used to monitor and adjust therapy.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE who are prescribed UFH and/or LMWH who have baseline laboratory tests documented in their medical record.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with VTE who are prescribed UFH and LMWH who have appropriate laboratory tests (platelets, PTT for those on UFH) available to monitor and adjust therapy.

Venous thromboembolism (VTE) diagnosis and treatment: percentage of patients with any of these diagnosis – VTE, PE, DVT – indicating a complete list of medications was communicated to the next clinician of service when the patient is referred or transferred to another setting, service, practitioner or level of care within or outside the organization.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Dupras D, Bluhm J, Felty C, Hansen C, Johnson T, Lim K, Maddali S, Marshall P, Messner P, Skeik N. Venous thromboembolism diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jan. 90 p. [216 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1998 Jun (revised 2013 Jan)

Guideline Developer(s)

Institute for Clinical Systems Improvement - Nonprofit Organization

Guideline Developer Comment

The Institute for Clinical Systems Improvement (ICSI) comprises 50+ medical group and hospital members representing 9,000 physicians in Minnesota and surrounding areas, and is sponsored by five nonprofit health plans. For a list of sponsors and participating organizations, see the ICSI Web site.

Source(s) of Funding

- The Institute for Clinical Systems Improvement (ICSI) provided the funding for this guideline. The annual dues of the member medical groups and sponsoring health plans fund ICSI's work. Individuals on the work group are not paid by ICSI, but are supported by their medical group for this work.
- ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups, and sponsoring health plans review and provide feedback, but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Guideline Committee

Venous Thromboembolism Work Group

Composition of Group That Authored the Guideline

Work Group Members: Denise Dupras, MD (*Work Group Leader*) (Mayo Clinic) (Internal Medicine); Terry A. Johnson, MD (Allina Medical Clinic) (Family Medicine); Nedaa Skeik, MD, FACP, FSVM, RPVI (Allina Medical Clinic) (Vascular Medicine); Seema Maddali, MD, MHA (HealthEast Care System) (Internal Medicine); Peter Marshall, PharmD (HealthPartners Health Plan) (Pharmacy); Cindy Felty, NP (Mayo Clinic) (Internal Medicine); Kaiser Lim, MD (Mayo Clinic) (Pulmonology); Penny Messner, DNP, RN, ACNS-BC (Mayo Clinic) (Vascular Medicine); Jim Bluhm, MPH (Institute for Clinical Systems Improvement [ICSI]) (Team Director); Carmen Hansen, BSN (ICSI) (Project Manager)

Financial Disclosures/Conflicts of Interest

The Institute for Clinical Systems Improvement (ICSI) has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI policy regarding Conflicts of Interest is available at the ICSI Web site.

Disclosure of Potential Conflicts of Interest

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Guideline-Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

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Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Venous thromboembolism diagnosis and treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 Jan. 96 p.

Guideline Availability

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

Availability of Companion Documents

The following is available:

- Venous thromboembolism diagnosis and treatment. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement; 2013 Jan. 1 p. Electronic copies: Available in Portable Document Format (PDF) from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

In addition, the appendices of the original guideline document contain the following:

- Wells model of the clinical pretest probability of deep vein thrombosis (DVT)
- Model for predicting clinical pretest probability for pulmonary embolism (PE)
- Ventilation/perfusion (V/Q) lung imaging algorithm and annotations
- Diagnosis and treatment of upper extremity deep vein thrombosis
- A shared decision-making model

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on February 15, 2000. The information was verified by the guideline developer on March 15, 2000. This NGC summary was updated by ECRI on December 14, 2001 and verified by the guideline developer on January 9, 2002. The NGC summary was updated by ECRI on January 28, 2004, July 28, 2004, July 14, 2005, and May 10, 2006. This NGC summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This NGC summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute most recently on September 10, 2007. This NGC summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This NGC summary was updated by ECRI Institute on December 26, 2008 following the FDA advisory on Innohep (tinzaparin). This NGC summary was updated by ECRI Institute on September 16, 2009. This NGC summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This NGC summary was updated by ECRI Institute on October 15, 2010, July 1, 2011, and June 10, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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